EDITORIAL

Multiplex edited universal CAR T cells without the genomic cost

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In this issue of *Haematologica*, the study by Preece *et al*. presenting multiplex base-edited CAR38-T cells as an "off-the-shelf" platform, arrives at an inflection point in cellular immunotherapy.[1] After nearly a decade of remarkable clinical success with autologous chimeric antigen receptor T-cell (CAR-T) therapies, the field continues to struggle with slow manufacturing, high costs, and variable product quality, the factors that ultimately limit patients' access, with some patients deteriorating or dying before their CAR-T product is ready.[2] Efforts to generate allogeneic or "universal" CAR-T products aim to untether cell therapy from individualized production. Yet, the same immunoregulation that provides protection against pathogens, namely T-cell receptor (TCR)-mediated alloreactivity and human leukocyte antigen (HLA) mismatch, has made universal CAR-T development a formidable challenge. The study by Preece *et al*. directly confronts these barriers using precise base-editing to create a TCR-null, HLA-null, anti-CD38 CAR-T platform with enhanced allo-resilience. The result is a product that is immunologically "quiet", while remaining functionally potent.

Why CD38? Revisiting a familiar target

The transmembrane glycoprotein CD38 is a well-validated target in multiple myeloma, and anti-CD38 monoclonal antibodies have reshaped the therapeutic landscape. Yet, the CD38 expression across additional cells makes it attractive far beyond myeloma.[3] Targeting CD38 introduces the major challenge of fratricide among CD38-positive T cells.[4] The authors address this elegantly through base-editing-mediated disruption of CD38, which prevents fratricide and enables stable CAR38 expression. The antigen breadth is notable. CAR38-T cells demonstrated robust activity across B-cell, T-cell, and myeloid leukemias, suggesting a platform with the potential to treat malignancies currently underserved by CAR-T therapies, including T-cell neoplasms in which fratricide, product contamination, and antigen overlap have stymied progress.[5] Of note, CD38 is expressed on immature hematopoietic cells; therefore, hematopoietic toxicity with CAR38-T is expected and should be carefully monitored when advancing this therapy into clinical use.

A new concept: allo-defense as an engineered function

Perhaps the most intriguing element of the study is the demonstration that CAR38-T cells can actively eliminate CD38-expressing allo-reactive host cells in mixed lymphocyte cultures. Rather than passively evading host immunity, these universal CAR-T cells establish a controlled counterattack against the very cells that would mediate rejection. This "allo-defense" is a conceptual shift: an allogeneic therapy that not only avoids elimination but reshapes the immunological landscape to protect itself. While this phenomenon will require validation *in vivo*, it raises compelling possibilities. A universal CAR-T product with both anti-tumor and anti-rejection functions could reduce the need for heavy lymphodepletion, potentially improving tolerability and expanding access for older or frail patients.

When breaks become a problem

To generate immunologically quiet CAR-T cells, multiple genetic edits are required, and the way these edits are introduced has real consequences for genomic stability.[6] Double-strand breaks create structural instability in primary T cells. Nahmad *et al*. demonstrated this by targeting the TCR locus with CRISPR Cas9 and observing high rates of chromosome 14 loss in human T cells.[7] These chromosomal aberrations become even more pronounced when multiple edits are needed as in the case of allogeneic CAR-T cells. These findings were notable because the structural changes appeared quickly and remained detectable after expansion. Other groups have also shown that multiplex cutting increases translocations and larger rearrangements.[8,9] which reinforces the idea that the editing burden itself becomes the limiting factor. In this context, the use of base-editing becomes the practical solution. It enables parallel modifi-

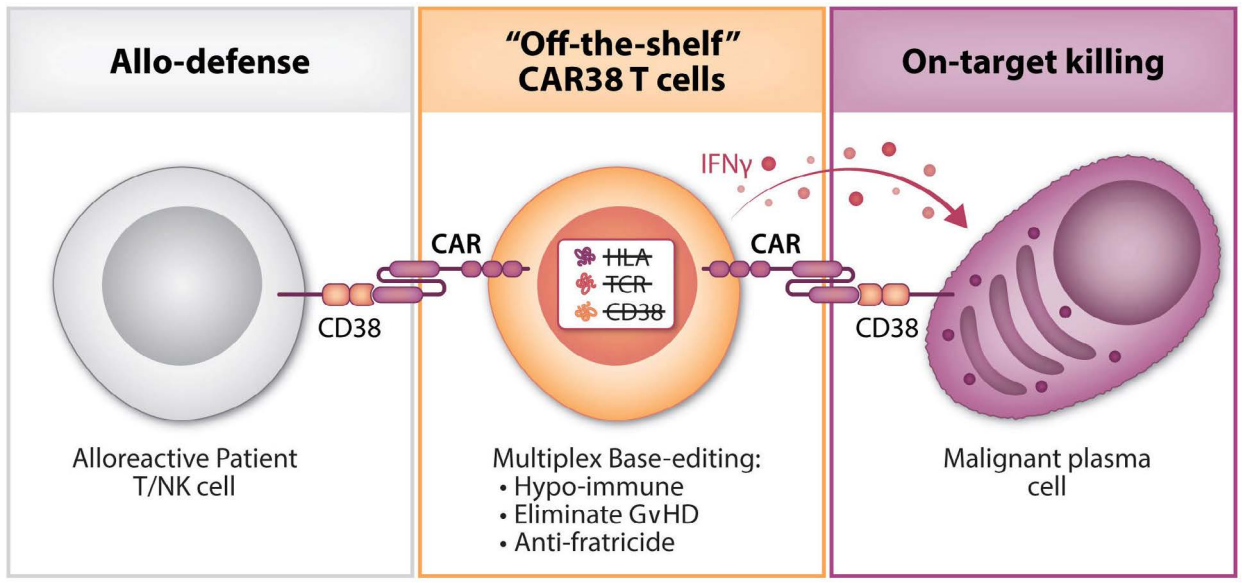

Figure 1. Conceptual model of base-edited CAR38-T cells. Multiplex base-editing disrupts TCR, HLA, and CD38 to generate hypo-immunogenic CAR38-T cells resistant to fratricide and graft-*versus*-host disease. These engineered cells retain cytotoxic activity against CD38⁺ malignant cells and can eliminate CD38⁺ alloreactive host T/NK cells, a phenomenon termed "allo-defense." Adapted from BioRender art.

cation of several loci without triggering the repair pathways that create chromosomal errors. This creates an editing framework that is better suited for designs that require coordinated disruption of TCR, HLA, and lineage markers in the same manufacturing run.

Why base-editing fits the allogeneic path

Allogeneic platforms rely on third-party donors, and once a donor is established, every manufactured dose inherits the same genomic background. Regulators evaluate these products as standardized biologics rather than individualized treatments, which places real weight on genomic consistency. Base-editing supports this expectation because it produces a more stable and predictable edit profile and reduces the chance of structural variants that would complicate release testing. It also allows developers to qualify a donor bank with greater confidence, since the product is less likely to accumulate editing-related chromosomal errors across batches. This is important for any multi-edited design, but especially for universal CAR-T programs that depend on simultaneous changes in TCR, HLA class I and II, and target antigens. The approach described in the study aligns with where allogeneic cell therapy is heading. A well-characterized donor and an editing strategy that minimizes genomic disruption create a practical route for advancing complex engineered products into clinical use.

Clinical promise and questions ahead

The *in vivo* xenograft models demonstrate clear antileukemic activity, but several translational challenges remain. Base-editing may alter differentiation pathways or metabolic fitness. Durable remission in humans will require long-lived, functionally competent cells and achieving this in an HLA-deficient context is not trivial. The capacity to target pathogenic plasma cells invites potential applications in autoimmunity. However, depletion of healthy long-lived plasma cells raises concerns about sustained hypogammaglobulinemia and risk of infection.[10]

Each of these hurdles is addressable, and the field is evolving rapidly. This CAR38 platform represents one of the most comprehensive attempts to engineer a universal cell therapy with functional, immunological, and safety considerations built into its DNA. Universal CAR-T cells will not replace autologous therapies overnight. But studies like this one by Preece *et al*. - precise, intentional, and mechanistically grounded - demonstrate that the path forward is no longer theoretical. It is engineered, multiplexed, and increasingly achievable.

Disclosures

No conflicts of interest to disclose.

Contributions

OB-K and ES contributed equally.

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